1: J Heart Lung Transplant. 1998 Apr;17(4):356-62.

Links

Circulating tumor necrosis factor-alpha levels in chronic heart failure: relation to its soluble receptor II, interleukin-6, and neurohumoral variables.

Koller-Strametz J, Pacher R, Frey B, Kos T, Woloszczuk W, Stanek B.

Department of Cardiology, University of Vienna, Austria.

The cytokines tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) are increased in the circulation of patients with chronic heart failure. However, their correlation with left ventricular dysfunction has not yet been thoroughly evaluated, and their interrelation with other neurohumoral systems, such as the adrenergic system and endothelin, is unclear. Therefore TNF-alpha, its soluble receptor II, IL-6, big endothelin, and noradrenaline levels were simultaneously measured in venous blood from 65 patients with heart failure in New York Heart Association (NYHA) class II to IV during therapy with digitalis, furosemide, and enalapril. TNF-alpha plasma levels were 3.2+/-0.2 SEM pg/ml in 38 patients in NYHA function class II, 4.0+/-0.3 SEM pg/ml in 16 patients in NYHA function class III, and 5.3+/-0.9 SEM pg/ml in 11 patients in NYHA function class IV ($p < 0.001$ vs NYHA function class II). IL-6 plasma levels were 3.1+/-0.6 SEM pg/ml in 38 patients in NYHA function class II, 5.2+/-0.8 SEM pg/ml in 16 patients in NYHA function class III, and 13.3+/-3.9 SEM pg/ml in 11 patients in NYHA function class IV ($p < 0.0001$ vs NYHA function class II and$p < 0.0001$ vs NYHA class III). Thus both cytokines increased with increasing severity of heart failure, but only IL-6 plasma levels were different in patients in the more severe function classes. TNF-alpha correlated closely with TNF soluble receptor II ($r = 0.8$, $p < 0.0001$) and modestly with serum creatinine ($r = 0.6$, $p < 0.0001$), whereas IL-6 plasma levels were not statistically related to kidney function. Significant modest correlations were also found among TNF-alpha and IL-6 ($r = 0.3$, $p < 0.01$), big endothelin ($r = 0.3$, $p < 0.01$), and noradrenaline levels ($r = 0.4$, <0.001). This study supports the hypothesis that in heart failure both cytokines, TNF-alpha, and IL-6, as well as neurohumoral factors, play a role in the clinical progression of the disease. Thereby levels of TNF-alpha but not IL-6 seem to be related to concomitant kidney

dysfunction.

PMID: 9588580 [PubMed - indexed for MEDLINE]

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☐	L12	L11 and (heart)adj(failure)	153
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☐	L10	(ursodeoxycholic)adj(acid)same(combination)	274
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☐	L6	L5 and endotoxin	2469
☐	L5	(heart)adj(failure)	29762
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L5 ANSWER 1 OF 21 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
2004:858866 The Genuine Article (R) Number: 857AX. Reduced oncotic necrosis in Fas receptor-deficient C57BL/6J-lpr mice after bile duct ligation. Gujral J S; Liu J; Farhood A; Jaeschke H (Reprint). Univ Arizona, Coll Med, Liver Res Inst, 1501 N Campbell Ave, Room 6309, Tucson, AZ 85724 USA (Reprint); Univ Arkansas Med Sci, Dept Pharmacol & Toxicol, Little Rock, AR 72205 USA; NIEHS, Inorgan Carcinogenesis Sect, NCI, Res Triangle Pk, NC 27709 USA; Univ Texas, Hlth Sci Ctr, Dept Pathol, Houston, TX USA. Jaeschke@email.arizona.edu. HEPATOLOGY (OCT 2004) Vol. 40, No. 4, pp. 998-1007. ISSN: 0270-9139. Publisher: JOHN WILEY & SONS INC, 111 RIVER ST, HOBOKEN, NJ 07030 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Neutrophils aggravate cholestatic liver injury after bile duct ligation (BDL). Recently, it was suggested that hepatocellular apoptosis might be critical for liver injury in this model. To test the hypothesis that apoptosis could be a signal for neutrophil extravasation and injury, we assessed parameters of apoptosis and inflammation after BDL using 2 different approaches: (1) wild-type and Fas receptor-deficient lpr mice of the C57BL/6J or C3H/HeJ strains, and (2) treatment with the pancaspase inhibitor z-Val-Ala-Asp-fluoromethylketone (z-VAD-fmk)in C3HeB/FeJ mice. After BDL for 3 days, total cell death was estimated to be between 10% and 50% of all cells evaluated. However, less than 0.1% of hepatocytes showed apoptotic morphology in all 3 strains. Processing of procaspase-3, caspase-3 enzyme activities, and immunohistochemical staining for cytokeratin 18 cleavage products indicated no activation of caspases. Real-time reverse-transcriptase polymerase chain reaction analysis revealed increased expression of many inflammatory mediators but no effect on proapoptotic genes. More than 50% of all accumulated neutrophils were extravasated and colocalized with foci of oncotic hepatocytes and chlorotyrosine adducts. z-VAD-fmk treatment had no effect on apoptosis or liver injury after BDL but eliminated apoptosis

after galactosamine/endotoxin in C3HeB/FeJ mice. In Fas receptor-deficient lpr mice (C57BL/6J), expression of inflammatory mediators, neutrophil accumulation and extravasation, chlorotyrosine adduct formation, and liver injury were reduced. This protection was not observed in lpr mice of the endotoxin-resistant C3H/HeJ strain. In conclusion, liver injury (oncotic necrosis) after BDL correlated with the severity of the inflammatory response. The minimal amount of apoptosis had no effect on inflammation or on the overall injury.

L5 ANSWER 2 OF 21 EMBASE

2004368727 EMBASE Pharmacologic management of nonalcoholic fatty liver disease. Harrison S.A.; Neuschwander-Tetri B.A.. Dr. S.A. Harrison, Brooke Army Medical Center, Dept. of Gastroenterol. and Hepatol., 3851 Roger Brooke Dr., Ft. Sam 78234, Houston, TX, United States. Stephen.Harrison@cen.amedd.army.mil. Clinics in Liver Disease Vol. 8, No. 3, pp. 715-728 2004.
Refs: 75.
ISSN: 1089-3261. CODEN: CLDIF
S 1089-3261(04)00041-8. Pub. Country: United States. Language: English.
Summary Language: English.
Entered STN: 20040916. Last Updated on STN: 20040916

AB Although many potential therapies have been studied,no proven therapy for NAFLD has been subjected to a large-scale, randomized clinical trial with adequate study duration and appropriate histopathologic end-points and follow up. However, several large-scale studies, using some of the therapeutic agents mentioned previously, are beginning to be put together through collaborative networks, some of which are sponsored by the National Institutes of Health in the form of the Clinical Research Network. Additionally, as our understanding of the pathogenesis of this disease becomes clearer, newer therapeutic targets will become available. A potential role for such therapies as probiotics to reduce bacterial endotoxin levels and antihypertensive agents such as angiotension II receptor blockers seem possible. Also, specific diets that improve insulin resistance coupled with combination pharmacotherapy that reduces oxidative stress and improves insulin use may be attractive options in the near future. At the present time, while these studies are being conducted, what should physicians be doing for their patients with NAFLD? If a patient with NAFLD is thought to clinically have mild disease, then recommendations of weight reduction are advocated, with a goal to lose at least 10% of body weight. A steady regular exercise program would assist in improving insulin use, as would a diet that consists of reduced, but not eliminated, carbohydrates. At the present time, with the possible exception of vitamin E, pharmacotherapy should be limited to those patients enrolling in clinical trials to assess the efficacy of therapy in a formal fashion. If patients have clinical evidence of advanced liver disease, one may be tempted to be more aggressive with their management, but again these patients should be encouraged to consider enrolling in a clinical trial to formally assess any potential pharmacotherapy.

L5 ANSWER 3 OF 21 EMBASE

2004132979 EMBASE Primary sclerosing cholangitis. Mendes F.D.; Lindor K.D.. Dr. K.D. Lindor, Div. of Gastroenterol. and Hepatol., Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, United States. lindor.keith@mayo.edu. Clinics in Liver Disease Vol. 8, No. 1, pp. 195-211 2004.
Refs: 96.
ISSN: 1089-3261. CODEN: CLDIF
S 1089-3261(03)00127-2. Pub. Country: United States. Language: English.
Summary Language: English.
Entered STN: 20040412. Last Updated on STN: 20040412

AB Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease associated with significant morbidity and mortality. Its

pathogenesis remains poorly understood, and that lack of understanding in part explains the lack of proven therapy able to modify the disease progression. Liver transplantation remains the only life-extending option for these patients. PSC is currently one of the most common indications for liver transplantation in the United States.

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2004079588 EMBASE Endotoxinemia and benzodiazepine-like substances in compensated cirrhotic patients: A randomized study comparing the effect of rifaximine alone and in association with a symbiotic preparation.

Lighthouse J.; Naito Y.; Helmy A.; Hotten P.; Fuji H.; Min C.H.; Yoshioka M.; Marotta F.. F. Marotta, via Pisanello 4, Milan 20146, Japan. fmarchimede@libero.it. Hepatology Research Vol. 28, No. 3, pp. 155-160 2004.

Refs: 31.

ISSN: 1386-6346. CODEN: HPRSFM

S 1386-6346(03)00438-8. Pub. Country: Ireland. Language: English. Summary Language: English.

Entered STN: 20040304. Last Updated on STN: 20040304

AB Aim: The aim of the present investigation was to test study benzodiazepines (BZDs) profile in patients with viral cirrhosis under different combinations of rifaximine and of a novel symbiotic. Methods: Our study groups consisted of 30 patients with a confirmed diagnosis of HCV-related Child B liver cirrhosis. Patients were randomly allocated into three groups: rifaximine 400 mg t.i.d. for 2 weeks; (B) SCM-III (Lactobacillus acidophilus, Lactobacillus helveticus and Bifidobacteria in a ion- and vitamin-enriched medium, Named srl, Italy) 10 ml t.i.d. for 2 weeks; (C) rifaximine 400 mg t.i.d. for 1 week followed by SCM-III 10 ml t.i.d. for 5 weeks. At weekly interval, blood samples were withdrawn to test BZD-like substances, ammonia and endotoxin. Results: Rifaximine treatment brought about a significant early drop of BZDs ($P<0.01$ versus pre-treatment and versus control) till fourth week of observation when a gradual increase took place with return to pre-treatment values at the sixth week. Symbiotic treatment was comparably effective while given to patients but significantly elevated BZDs level were noted starting from the third week. Similar phenomena were noted for endotoxin and ammonia although symbiotic seemed more effective against endotoxin and rifaximine against ammonia increase. However, the sequential treatment rifaximine-symbiotic brought about a sustained normalization of BZDs, ammonia and endotoxin throughout the 6-week study. Conclusion: The present pilot study suggests that a rifaximine-symbiotic regimen could be an effective tool in compensated liver cirrhosis to limit some triggering factors of hepatic encephalopathy while being amenable to long-term use and devoid of significant side effects. .COPYRGT. 2003 Elsevier B.V. All rights reserved.

L5 ANSWER 5 OF 21 MEDLINE on STN DUPLICATE 1

2004098209. PubMed ID: 14987744. Immune response to lipopolysaccharide in primary biliary cirrhosis and autoimmune diseases. Ballot Eric; Bandin Olivia; Chazouilleres Olivier; Johanet Catherine; Poupon Raoul. (Service d'Immunologie, Hopital Saint-Antoine, AP-HP, 184 rue du faubourg Saint-Antoine, 75012 Paris, France.) Journal of autoimmunity, (2004 Mar) Vol. 22, No. 2, pp. 153-8. Journal code: 8812164. ISSN: 0896-8411. Pub. country: England: United Kingdom. Language: English.

AB A bacteriological aetiology is suspected to be the triggering factor in primary biliary cirrhosis. We studied lipid A, the toxic and immunogenic moiety of gram-negative bacteria lipopolysaccharide, which accumulates abnormally in Kupffer cells, hepatocytes, and biliary epithelial cells in primary biliary cirrhosis patients. Anti-lipid A antibody levels from serum samples from 36 primary biliary cirrhosis patients, drawn before and after ursodeoxycholic acid treatment, were compared to those from patients with other liver diseases (n=236),

non-hepatic diseases (n=249), and healthy subjects (n=75). In primary biliary cirrhosis patients, the prevalence of IgM anti-lipid A antibodies was higher before than after ursodeoxycholic acid therapy (64% vs 22%, respectively; P<0.001). Patients with anti-lipid A antibodies had significantly higher IgM levels than those without antibodies (8.7+/-1.1 g/l vs 4.4+/-0.8 g/l, P<0.02). Total IgM levels were correlated with anti-lipid A antibody levels (r=0.65, P<0.02). After therapy, the serum IgM levels decreased significantly (P<0.03). These results indicate that bacterial antigens may participate in the observed increase of serum IgM levels, and support an aetiological role of a gut-derived endotoxin antigen in the pathogenesis of primary biliary cirrhosis.

L5 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2006 ACS on STN
2003:691815 Document No. 139:240624 Growth hormone modulation of the rat hepatic bile transporter system in endotoxin-induced cholestasis. Mesotten, Dieter; Van den Berghe, Greet; Liddle, Christopher; Coulter, Sally; McDougall, Fiona; Baxter, Robert C.; Delhanty, Patric J. D. (Kolling Institute of Medical Research, Royal North Shore Hospital, University of Sydney, St. Leonards, 2065, Australia). Endocrinology, 144(9), 4008-4017 (English) 2003. CODEN: ENDOAO. ISSN: 0013-7227. Publisher: Endocrine Society.

AB Treatment with high dose human GH, although an effective anabolic agent, has been associated with increased incidence of sepsis, inflammation, multiple organ failure, and death in critically ill patients. The authors hypothesized that GH might increase mortality by exacerbating cholestasis through modulation of bile acid transporter expression. High dose GH was continuously infused over 4 d into rats, and on the final day lipopolysaccharides were injected. Hepatic bile acid transporter expression was measured by Northern anal. and immunoblotting and compared with serum markers of cholestasis and endotoxinemia. Compared with non-GH-treated controls, GH increased endotoxin -induced markers of cholestasis and liver damage as well as augmented IL-6 induction. In endotoxinemia, GH treatment significantly induced multidrug resistance-associated protein 1 mRNA and protein and suppressed organic anion transporting polypeptides, Oatp1 and Oatp4, mRNA, suggesting impaired uptake of bilirubin and bile acids at the basolateral surface of the hepatocyte, which could contribute to the observed worsening of cholestasis by GH. This study of endotoxinemia may thus provide a mechanistic link between GH treatment and exacerbation of cholestasis through modulation of basolateral bile acid transporter expression in the rat hepatocyte.

L5 ANSWER 7 OF 21 MEDLINE on STN DUPLICATE 2
2004248991. PubMed ID: 15146603. [Molecular mechanisms of bile formation and cholestatic diseases]. Mecanismes moleculaires de la formation de la bile et des maladies cholestatiques. Poupon Raoul. (Service d'Hepatologie, Hopital Saint-Antoine, AP Hopitaux de Paris 184, rue du Faubourg Saint-Antoine-75571 Paris.) Bulletin de l'Academie nationale de medecine, (2003) Vol. 187, No. 7, pp. 1261-74; discussion 1274-6. Ref: 51. Journal code: 7503383. ISSN: 0001-4079. Pub. country: Netherlands. Language: French.

AB Biliary function is a vital function of the liver which results from the vectorial transport of endogenous and exogenous substrates through three compartments sequentially: the vascular space, the cellular space and the biliary space. The biliary function is responsible for the homeostasis of lipid metabolism in particular of cholesterol metabolism, the elimination of toxic endo--and xenobiotics such as (bilirubin, lipid bacteria products (endotoxin)) and several inflammatory mediators. Bile elaborated in canaliculi, is modified by cholangiocytes through secretion and absorption. Bile is essential for the intestinal digestion and absorption of nutriments. The main determinant of bile formation is an osmotic filtration process resulting from active transport of bile acids and other osmotic solutes (glutathione). Most of the membrane

transporters ensuring bile formation have now been identified. The expression of these membrane transporters is regulated through transcriptional and post-tranductional mechanisms. Transcriptional regulation is under the control of nuclear receptors activated by ligands such as bile acids, which act as endogenous steroids synthesized from cholesterol in hepatocytes. Cholestatic liver diseases comprise genetic diseases resulting from the complex interaction between genetic and environmental factors. Monogenic cholestatic diseases recently identified illustrate the key role of membrane transporters in biliary function. Bile acids and inflammatory mediators are potent modulators transporters and nuclear receptor genes and thus trigger an adaptative response to cholestasis. The extent of this adaptative response could explain the compelling phenotypic variability of cholestatic diseases in childhood and adults. The firstline medical treatment is currently ursodeoxycholic acid and in case of failure of this medical treatment, liver transplantation is required. Recent progress in the molecular pathogenesis of bile formation and cholestatic liver diseases is expected to provide the design of drugs targeted to the molecular abnormalities typical of cholestatic diseases.

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2003:885587 The Genuine Article (R) Number: 728TB. Loss of inositol 1,4,5-trisphosphate receptors from bile duct epithelia is a common event in cholestasis. Shibao K; Hirata K; Robert M E; Nathanson M H (Reprint). Yale Univ, Sch Med, Dept Internal Med, New Haven, CT 06510 USA (Reprint); Yale Univ, Sch Med, Dept Pathol, New Haven, CT 06510 USA. GASTROENTEROLOGY (OCT 2003) Vol. 125, No. 4, pp. 1175-1187. ISSN: 0016-5085. Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background & Aims: Cholestasis is one of the principal manifestations of liver disease and often results from disorders involving bile duct epithelia rather than hepatocytes. A range of disorders affects biliary epithelia, and no unifying pathophysiologic event in these cells has been identified as the cause of cholestasis. Here we examined the role of the inositol :1,4,5-trisphosphate receptor (InsP3R)/Ca2+ release channel in Ca2+ signaling and ductular secretion in animal models of cholestasis and in patients with cholestatic disorders. Methods: The expression and distribution of the InsP3R and related proteins were examined in rat cholangiocytes before and after bile duct ligation or treatment with endotoxin. Ca2+ signaling was examined in isolated bile ducts from these animals, whereas ductular bicarbonate secretion was examined in isolated perfused livers. Confocal immunofluorescence was used to examine cholangiocyte InsP3R expression in human liver biopsy specimens. Results: Expression of the InsP3R was selectively lost from biliary epithelia after bile duct ligation or endotoxin treatment. As a result, Ca2+ signaling and Ca2+-mediated bicarbonate secretion were lost as well, although other components of the Ca2+ signaling pathway and adenosine 3',5'-cyclic monophosphate (cAMP)mediated bicarbonate secretion both were preserved. Examination of human liver biopsy specimens showed that InsP3Rs also were lost from bile duct epithelia in a range of human cholestatic disorders, although InsP3R expression was intact in noncholestatic liver disease. Conclusions: InsP3-mediated Ca2+ signaling in bile duct epithelia appears to be important for normal bile secretion in the liver, and loss of InsP3Rs may be a final common pathway for cholestasis.

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2003016817 EMBASE Oxidative stress in viral and alcoholic hepatitis. Loguercio C.; Federico A.. Prof. C. Loguercio, Catt. Gastroenterol. II Univ. Napoli, Via Pansini 5, 80131 Napoli, Italy. caloguer@tin.it. Free Radical Biology and Medicine Vol. 34, No. 1, pp. 1-10 1 Jan 2003.

Refs: 139.
ISSN: 0891-5849. CODEN: FRBMEH
S 0891-5849(02)01167-X. Pub. Country: United States. Language: English.
Summary Language: English.
Entered STN: 20030129. Last Updated on STN: 20030129

AB Liver damage ranges from acute hepatitis to hepatocellular carcinoma, through apoptosis, necrosis, inflammation, immune response, fibrosis, ischemia, altered gene expression and regeneration, all processes that involve hepatocyte, Kupffer, stellate, and endothelial cells. Reactive oxygen and nitrogen species (ROS, RNS) play a crucial role in the induction and in the progression of liver disease, independently from its etiology. They are involved in the transcription and activation of a large series of cytokines and growth factors that, in turn, can contribute to further production of ROS and RNS. The main sources of free radicals are represented by hepatocyte mitochondria and cytochrome P450 enzymes, by endotoxin-activated macrophages (Kupffer cells), and by neutrophils. The consequent alteration of cellular redox state is potentiated by the correlated decrease of antioxidant and energetic reserves. Indices of free radical-mediated damage, such as the increase of malondialdehyde, 4-hydroxynonenal, protein-adducts, peroxynitrite, nitrotyrosine, etc., and/or decrease of glutathione, vitamin E, vitamin C, selenium, etc., have been documented in patients with viral or alcoholic liver disease. These markers may contribute to the monitoring the degree of liver damage, the response to antiviral therapies and to the design of new therapeutic strategies. In fact, increasing attention is now paid to a possible "redox gene therapy." By enhancing the antioxidant ability of hepatocytes, through transgene vectors, one could counteract oxidative/nitrosative stress and, in this way, contribute to blocking the progression of liver disease. .COPYRGT. 2002 Elsevier Science Inc.

L5 ANSWER 10 OF 21 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 3

2001140092 EMBASE Endotoxin increases paracellular permeability of isolated rat hepatocyte couplets. Kawaguchi T.; Sakisaka S.; Harada M.; Hanada S.; Taniguchi E.; Koga H.; Sasatomi K.; Tanikawa K.; Sata M.. M. Harada, Second Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan. harada@med.kurume.u.ac.jp. Hepatology Research Vol. 20, No. 1, pp. 144-154 2001.
Refs: 26.
ISSN: 1386-6346. CODEN: HPRSFM
Pub. Country: Ireland. Language: English. Summary Language: English.
Entered STN: 20010503. Last Updated on STN: 20010503

AB Hyperbilirubinemia is frequently associated with endotoxemia. Regurgitation of bile constituents including bilirubin into the sinusoidal space is prevented by tight junctions which maintain paracellular permeability between hepatocytes. To investigate the mechanism of endotoxin-associated hyperbilirubinemia, we have studied the changes in paracellular permeability of primary hepatocyte couplets treated with endotoxin. In addition, we examined the effects of ursodeoxycholic acid (UDCA), which has been widely used for various liver diseases, on endotoxin-associated changes in paracellular permeability. The paracellular permeability of hepatocyte couples was evaluated by paracellular penetration of fluorescein isothiocyanate (FITC)-dextran with molecular weights of 3, 10 and 70K using confocal laser scanning microscopy. Endotoxin increased the paracellular penetration of FITC-dextran 3 and 10K. These changes were prevented by treatment with UDCA. There was little paracellular penetration of FITC-dextran 70K under any conditions. These results suggested that endotoxin increased the paracellular permeability of hepatocyte couplets and these changes were prevented by treatment with UDCA. Furthermore, bile regurgitation through the paracellular route is involved in endotoxin-associated hyperbilirubinemia, and UDCA might be a potential therapeutic agent for

endotoxin-associated hyperbilirubinemia.

L5 ANSWER 11 OF 21 MEDLINE on STN DUPLICATE 4

2000191144. PubMed ID: 10728800. Chronic cholestatic diseases. Poupon R; Chazouilleres O; Poupon R E. (Service d'hepatogastroenterologie, Hopital Saint-Antoine, Paris, France.) Journal of hepatology, (2000) Vol. 32, No. 1 Suppl, pp. 129-40. Ref: 120. Journal code: 8503886. ISSN: 0168-8278. Pub. country: Denmark. Language: English.

AB Chronic cholestatic diseases, whether occurring in infancy, childhood or adulthood, are characterized by defective bile acid transport from the liver to the intestine, which is caused by primary damage to the biliary epithelium in most cases. In this article, approaches to diagnosis and management of the main specific disorders are provided and some of the recent developments in this field are discussed. Major advances in the understanding of the cellular and molecular physiology of bile secretion have led to identification of genetic defects responsible for the different types of progressive familial intrahepatic cholestasis (PFIC). The potential role of the genes involved in PFIC in some adult cholestatic disorders remains to be determined. The majority of adult patients with chronic cholestasis have primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC). Recently, variant forms of PBC have been described. The term autoimmune cholangitis is used to describe patients having chronic non-suppurative cholangitis with negative antimitochondrial antibodies (AMA) but positive antinuclear and/or antismooth muscle antibodies. Autoimmune cholangitis and AMA-positive PBC are quite similar in terms of clinical presentation, survival and response to ursodeoxycholic acid (UDCA) therapy. In contrast, autoimmune cholangitis must be distinguished from PBC-autoimmune hepatitis (AIH) overlap syndrome in which biochemical and histological characteristics of both PBC and AIH coexist. Combination of UDCA and corticosteroids is required in most patients with overlap syndrome to obtain a complete clinical and biochemical response. Long-term UDCA treatment improves survival without liver transplantation in PBC patients. Among the putative mechanisms of the beneficial effects of UDCA, description of anti-apoptotic properties and effect on endotoxin disposal in biliary cells have provided new insights. In patients with incomplete response to UDCA, combination of UDCA with antiinflammatory or immunosuppressive drugs is under evaluation. Variant forms of PSC have also been described, including PSC-AIH overlap syndrome, especially in children or young adults, and small-duct PSC, which is characterized by normal cholangiogram in patients having chronic cholestasis, histologic features compatible with PSC and inflammatory bowel disease. Development of cholangiocarcinoma (CC) is a major feature of PSC, occurring in 10-15% of patients. Early diagnosis of CC is a difficult challenge, although positron emission tomography seems a promising tool. Unlike PBC, effective medical therapy is not yet available in PSC, reflecting the lack of knowledge about the exact pathogenesis of the disease. Currently, liver transplantation is the only effective therapy for patients with advanced disease, although recurrence of PSC in the graft may occur.

L5 ANSWER 12 OF 21 MEDLINE on STN DUPLICATE 5

1999390428. PubMed ID: 10461327. New approaches to understanding the etiology and treatment of total parenteral nutrition-associated cholestasis. Moss R L; Amii L A. (Department of Surgery, Stanford University School of Medicine, CA, USA.) Seminars in pediatric surgery, (1999 Aug) Vol. 8, No. 3, pp. 140-7. Ref: 101. Journal code: 9216162. ISSN: 1055-8586. Pub. country: United States. Language: English.

AB Total parenteral nutrition-associated cholestasis (TPN-AC) may be a fatal disease. The only known effective treatment is to discontinue TPN and institute full enteral feedings. However, this is not possible for many patients with severe gastrointestinal failure. Current research supports two theories regarding the etiology of TPN-AC. One proposes that

the enteral fast disrupts the enterohepatic circulation. Cholestasis, in this hypothesis, results from a combination of altered gut hormone production and endotoxins produced by bacterial translocation.
The second theory implicates the direct toxicity of TPN solution. Amino acid solutions and plant sterols in intralipid have generated much interest. Ursodeoxycholic acid and
S-adenosyl-L-methionine are promising treatments for TPN-AC.
They have been proven to be effective in animals and adult liver diseases. Cholecystokinin also has been investigated as a possible prophylactic agent. However, results from these experiments do not conclusively show a beneficial effect.

L5 ANSWER 13 OF 21 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1998:536965 The Genuine Article (R) Number: ZY285. Stimulation of bile duct epithelial secretion by glibenclamide in normal and cholestatic rat liver. Nathanson M H (Reprint); Burgstahler A D; Mennone A; Dranoff J A; Rios-Velez L. Yale Univ, Sch Med, Liver Study Unit, Room 1080 LMP, 333 Cedar St, New Haven, CT 06520 USA (Reprint); Yale Univ, Sch Med, Liver Study Unit, New Haven, CT 06520 USA; Yale Univ, Sch Med, Dept Cell Biol, New Haven, CT 06520 USA. JOURNAL OF CLINICAL INVESTIGATION (15 JUN 1998) Vol. 101, No. 12, pp. 2665-2676. ISSN: 0021-9738. Publisher: AMER SOC CLINICAL INVESTIGATION INC, 35 RESEARCH DR, STE 300, ANN ARBOR, MI 48103 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cholestasis is a cardinal complication of liver disease, but most treatments are merely supportive. Here we report that the sulfonylurea glybenclamide potently stimulates bile flow and bicarbonate excretion in the isolated perfused rat liver. Video-microscopic studies of isolated hepatocyte couplets and isolated bile duct segments show that this stimulatory effect occurs at the level of the bile duct epithelium, rather than through hepatocytes. Measurements of cAMP, cytosolic pH, and Ca2+ in isolated bile duct cells suggest that glybenclamide directly activates Na+-K+-2Cl(-) cotransport, rather than other transporters or conventional second-messenger systems that link to secretory pathways in these cells. Finally, studies in livers from rats with endotoxin - or estrogen-induced cholestasis show that glybenclamide retains its stimulatory effects on bile flow and bicarbonate excretion even under these conditions. These findings suggest that bile duct epithelia may represent an important new therapeutic target for treatment of cholestatic disorders.

L5 ANSWER 14 OF 21 MEDLINE on STN DUPLICATE 6

1998436016. PubMed ID: 9764987. Abnormal accumulation of endotoxin in biliary epithelial cells in primary biliary cirrhosis and primary sclerosing cholangitis. Sasatomi K; Noguchi K; Sakisaka S; Sata M; Tanikawa K. (Second Department of Medicine, Kurume University School of Medicine, Japan.) Journal of hepatology, (1998 Sep) Vol. 29, No. 3, pp. 409-16. Journal code: 8503886. ISSN: 0168-8278. Pub. country: Denmark. Language: English.

AB BACKGROUNDS/AIMS: Previous studies have revealed the involvement of Kupffer cells and hepatocytes in the metabolism of endotoxin in the liver. The aim of this study was to investigate the in vivo localization of endotoxin in liver cells, including Kupffer cells, hepatocytes, and biliary epithelial cells, in primary biliary cirrhosis and primary sclerosing cholangitis. We also examined the effect of ursodeoxycholic acid on the intrahepatic distribution of endotoxin in primary biliary cirrhosis.
METHODS: The immunohistochemical localization of endotoxin was examined in liver specimens from 30 cases of primary biliary cirrhosis and seven of primary sclerosing cholangitis using a monoclonal antibody against lipid A. Controls were seven cases of obstructive jaundice, ten of hepatitis C virus-related liver cirrhosis, 14 of chronic hepatitis C, and five histologically normal liver cases. Semi-quantitative analysis of

endotoxin accumulation was performed to measure the intensity of fluorescence for endotoxin. Nine of the 30 patients with primary biliary cirrhosis underwent a second liver biopsy for evaluation of the ursodeoxycholic acid treatment.
RESULTS: In primary biliary cirrhosis and primary sclerosing cholangitis, biliary epithelial cells showed strong immunostaining for endotoxin as well as hepatocytes and Kupffer cells. Biliary epithelial cells of primary biliary cirrhosis and primary sclerosing cholangitis showed more intense immunoreactivity than those of other controls. In primary biliary cirrhosis, ursodeoxycholic acid reduced the immunoreactivity to endotoxin in biliary epithelial cells, and increased the immunoreactivity to endotoxin in Kupffer cells, but did not affect that in hepatocytes. CONCLUSIONS: Our results revealed that in primary biliary cirrhosis and primary sclerosing cholangitis, endotoxin accumulates abnormally in biliary epithelial cells. In addition, we found that ursodeoxycholic acid treatment in primary biliary cirrhosis may provide a beneficial effect on the intrahepatic metabolism of endotoxin.

L5 ANSWER 15 OF 21 MEDLINE on STN DUPLICATE 7
1998290062. PubMed ID: 9626760. Biliary secretion of endotoxin and pathogenesis of primary biliary cirrhosis. Sakisaka S; Koga H; Sasatomi K; Mimura Y; Kawaguchi T; Tanikawa K. (Second Department of Medicine, Kurume University School of Medicine, Japan.. sakisaka@med.kurume-u.ac.jp) . The Yale journal of biology and medicine, (1997 Jul-Aug) Vol. 70, No. 4, pp. 403-8. Ref: 12. Journal code: 0417414. ISSN: 0044-0086. Pub. country: United States. Language: English.
AB Previous studies suggested endotoxin, derived from the intestine through the portal blood to the liver, was predominantly metabolized by Kupffer cells. In the present study, fluorescent-labeled endotoxin injected into the rat portal vein was demonstrated not only in Kupffer cells but also in hepatocytes. Furthermore a great amount of labeled endotoxin was recovered in bile. In the livers of patients with primary biliary cirrhosis (PBC), immunohistochemistry demonstrated significant retention of endotoxin in the biliary epithelial cells, and treatment with ursodeoxycholic acid significantly reduced the retention in those cells. The study for detection of apoptosis demonstrated increased rates of apoptosis in hepatocytes and biliary epithelial cells in PBC liver, and the rate of apoptosis in biliary epithelial cells was significantly reduced after treatment with ursodeoxycholic acid.
Immunohistochemistry in PBC liver demonstrated significant reduction of fluorescence intensity for a 7H6 antigen in biliary epithelial cells, indicating the increased paracellular permeability of bile ducts, because cellular immunolocalization of that antigen has been shown to be inversely correlated with the paracellular permeability of the tight junction. These results suggest that, in biliary epithelial cells, retention of endotoxin, increased apoptosis, and increased permeability of tight junctions may be involved in the pathogenesis of PBC.

L5 ANSWER 16 OF 21 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
1997:238318 The Genuine Article (R) Number: WN979. A clinical hepatologist's predictions about non-absorbed carbohydrates for the early twenty-first century. Conn H O (Reprint). YALE UNIV, SCH MED, 333 CEDAR ST, NEW HAVEN, CT 06520 (Reprint); DEPT VET AFFAIRS MED CTR, W HAVEN, CT 06512. SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY (1997) Vol. 32, Supp. [222], pp. 88-92. ISSN: 0036-5521. Publisher: SCANDINAVIAN UNIVERSITY PRESS, PO BOX 2959 TOYEN, JOURNAL DIVISION CUSTOMER SERVICE, N-0608 OSLO, NORWAY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB To put these predictions into perspective, the primary indication for lactulose therapy in the treatment of HE and SHE is presented

and discussed. Six secondary indications for lactulose therapy are also listed and briefly commented upon. A dozen predictions about the status of lactulose are presented and briefly discussed. A. Lactulose will be the treatment of choice for HE. B. TIPS will be the most common cause of HE. C. Lactulose will not be approved in Mexico. D. Lactulose plus anti-diarrheal drugs will be agents for treatment of HE. E. Lactulose will be the treatment of choice for constipation. F. Lactulose will not be used for Salmonella or Shigella carrier states. G. Lactulose will be routinely administered prophylactically after TIPS. H. Lactulose will be administered prophylactically to cirrhotic patients with portal hypertension. I. Lactulose plus anti-diarrheal drugs will be used for a variety of diverse purposes: (i) Suppression of bacterial growth; (ii) prevention of bacteriuria; (iii) diminution of cholesterol saturation of bile; (iv) adjunct treatment of gallstones with ursodeoxycholic acid; (v) prevention of colon carcinoma.

L5 ANSWER 17 OF 21 MEDLINE on STN DUPLICATE 8

95288486. PubMed ID: 7770639. Effects of ursodeoxycholic acid on hemodynamic and renal function abnormalities induced by obstructive jaundice in rats. Poo J L; Estanes A; Pedraza-Chaverri J; Cruz C; Uribe M. (Liver Unit, Instituto Nacional de la Nutricion Salvador Zubiran, Mexico City, Mexico.) Renal failure, (1995 Jan) Vol. 17, No. 1, pp. 13-20. Journal code: 8701128. ISSN: 0886-022X. Pub. country: United States. Language: English.

AB The mechanism of renal function abnormalities in experimental biliary cirrhosis can be partially explained by the absence of gastrointestinal bile flow, which predisposes to translocation of intestinal endotoxin, a potent renal vasoconstrictor. Since bile acids prevent the absorption of intestinal endotoxins, we aimed to evaluate the effects of ursodeoxycholic acid (UDCA) administration on renal function and hemodynamic abnormalities induced by 1 week of obstructive jaundice in rats. METHODS: Fifty-two rats were used; 30 had ligation of the common bile duct, 22 were sham operated. Bile duct ligated rats were randomly and blindly assigned to receive UDCA (25 mg/kg/day, n = 14) or placebo (n = 16) during 1 week. Sham rats received no treatment. Portal pressure (PP) as well as creatinine clearance (CrCl), urinary sodium (US), and plasma renin activity (PRA) were evaluated. Results are mean +/- SEM, with a significant value of $p < 0.05$. RESULTS: Portal pressure (10.4 +/- 1.1 vs. 12.1 +/- 0.8 mm Hg) was significantly lower in UDCA than in placebo-treated rats. ALT serum levels were also significantly lower in bile duct ligated rats receiving UDCA (77.3 +/- 28 IU/L) than in placebo-treated rats (162 +/- 65 IU/L). US (1.1 +/- 0.5 vs. 2.1 +/- 0.3 mEq/24 h) was significantly lower and PRA (6.0 +/- 2.6 vs. 1.9 +/- 1.0 ng Ang 1/mL/h) higher in bile duct ligated than in sham-operated rats. No differences were found between UDCA or placebo-treated bile duct ligated rats. CrCl was similar between sham (0.39 +/- 0.12 mL/min/100 g BW) and UDCA (0.32 +/- 0.16) but significantly lower in placebo-treated (0.28 +/- 0.07) than sham-operated rats ($p < 0.05$). CONCLUSION: UDCA administration had very mild effects on renal function abnormalities induced by experimental obstructive jaundice in rats. However, portal hypertension and biochemical abnormalities were partially improved.

L5 ANSWER 18 OF 21 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

94126399 EMBASE Document No.: 1994126399. Differential effects of chenodeoxycholic and ursodeoxycholic acids on expression of procoagulant activity by human monocytes. Calmus Y.; Podevin P.; Robert A.; Poupon R.. Hopital Cochin, 27, rue du Faubourg Saint-Jacques,75014 Paris, France. Journal of Hepatology Vol. 20, No. 4, pp. 466-472 1994.
ISSN: 0168-8278. CODEN: JOHEEC
Pub. Country: Denmark. Language: English. Summary Language: English.

Entered STN: 940608. Last Updated on STN: 940608

AB Cell-mediated immunity is impaired during cholestasis, and there is evidence for the involvement of endogenous bile acids. The aim of this study was to evaluate the effects of individual bile acids on immunity and to determine whether monocytes are a target. The effects of bile acids on the procoagulant activity of human monocytes, a lymphocyte-dependent model of monocyte activation, were assessed. Chenodeoxycholic acid, one of the main human primary bile acids, had a concentration-dependent inhibitory effect on procoagulant activity expressed by endotoxin -stimulated mononuclear cells, with half-maximal and maximal inhibitions at 100 and 250 μM, respectively. The inhibitory concentrations were similar for the procoagulant activity of unstimulated mononuclear cells and for endotoxin-stimulated isolated monocytes. In contrast, ursodeoxycholic acid, a bile acid which has beneficial effects in cholestatic diseases, had no significant inhibitory effects at concentrations up to 250 μM. These results indicate that endogenous bile acids tend to inhibit monocyte activation, suggesting a potential role for primary endogenous bile acids in the immune defect associated with cholestasis; ursodeoxycholic acid, which is devoid of effects on the immune system, may potentially reverse cholestasis-induced immunodeficiency.

L5 ANSWER 19 OF 21 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 9

94171031 EMBASE Document No.: 1994171031. The protective effect of the intravenous administation of ursodeoxycholic acid against endogenous endotoxemia in obstructive jaundiced rats. Nakatani M.. Second Department of Surgery, Kinki University School of Medicine,Osaka, Japan. Medical Journal of Kinki University Vol. 19, No. 1, pp. 109-118 1994.

ISSN: 0385-8367. CODEN: KDIZDD

Pub. Country: Japan. Language: Japanese. Summary Language: English.

Entered STN: 940706. Last Updated on STN: 940706

AB Endogenous endotoxemia, which is due to the facilitated bacterial translocation from intraluminal space of the gastrointestinal tract to portal vein in spite of the absence of a focus of infection, is possibly involved in poor biliary drainage of percutaneous transhepatic cholangiodrainage (PTCD) in the case of obstructive jaundice. Ursodeoxycholic acid (UDCA) is a bile acid, which is often orally used in the treatment of cholestasis. Herein, the protective effect of intravenous administration of UDCA against endotoxemia was determined by measuring the survival rate, endotoxin concentration in portal and peripheral veins, ATP content of rat liver and serum level of TNF-α. Endogenous endotoxemia in rats with obstructive jaundice induced by simultaneous administration of E. coli endotoxin orally at the dose of 5 mg/100 g body weight and lead acetate intravenously at the dose of 5 mg/100 g body weight following bile duct ligation for two weeks and recanaliculization thereafter according to the model of Bailey. UDCA administration at the dose of 0.05 μmol/100 g body weight/min improved the survival rate significantly. In the UDCA-treated group, the endotoxin concentration in the peripheral vein was significantly lower and ATP content was significantly recovered to the normal level. Conversely, the endotoxin concentration in the portal vein and serum level of TNF-α were not different between the UDCA-treated and saline-treated control rats. To investigate the mechanism of effect of UDCA on the secretion of endotoxin into bile, fluorescein isothiocyanate (FITC) labeled lipopolysaccharide (LPS) was administered via the portal vein and its concentration in bile was measured with a spectrophotofluorometer. A significant increase in the secretion of LPS into the bile was noticed in UDCA-treated rats, suggesting that the lower concentration of LPS in the peripheral vein in UDCA-treated rats depends on the increase in secretion of LPS into the bile. These findings demonstrate that intravenous administration of UDCA protects against

endotoxemia in obstructive jaundice by activating the transport pathway of endotoxin across the hepatocytes into the bile but has no effect on Kupffer cells. Therefore, UDCA treatment may be beneficial in the case of poor biliary drainage of PTCD in obstructive jaundice.

L5 ANSWER 20 OF 21 MEDLINE on STN DUPLICATE 10

89379032. PubMed ID: 2777206. Bile acids inhibit endotoxin -induced release of tumor necrosis factor by monocytes: an in vitro study. Greve J W; Gouma D J; Buurman W A. (Department of Surgery, Academic Hospital, University of Limburg, Maastricht, The Netherlands.) Hepatology (Baltimore, Md.), (1989 Oct) Vol. 10, No. 4, pp. 454-8. Journal code: 8302946. ISSN: 0270-9139. Pub. country: United States. Language: English.

AB Endotoxins play an important role in the pathogenesis of complications of surgery in obstructive jaundice. Preoperative treatment with orally administered deoxycholic acid prevented endotoxin-related complications, such as renal malfunction. Other bile acids, however, were less effective, and the mechanism of action is not known. Endotoxin toxicity is considered to be largely mediated by tumor necrosis factor/cachectin, a cytokine release by mononucler phagocytes. Therefore, we studied the influence of different bile acids on endotoxin-induced tumor necrosis factor production by monocytes in vitro. Bile acids inhibit tumor necrosis factor production through a direct inhibitory effect on the monocytes. Deoxycholic acid was the most effective, chenodeoxycholic acid was less effective and ursodeoxycholic acid was ineffective in the concentrations used. Bile acids did not inactivate endotoxin as measured in a chromogenic Limulus amebocyte lysate assay. The therapeutic effect of bile acids in obstructive jaundice can be explained by an inhibition of endotoxin-induced tumor necrosis factor release by mononuclear phagocytes.

L5 ANSWER 21 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

1998:326380 Document No.: PREV199800326380. Biliary secretion of endotoxin and pathogenesis of primary biliary cirrhosis. Sakisaka, S. [Reprint author]; Koga, H.; Sasatomi, K.; Mumura, Y.; Kawaguchi, T.; Tanikawa, K.. Second Dep. Med., Kurume Univ. School Med., 67 Asahi-Machi, Kurume 830-0011, Japan. Yale Journal of Biology and Medicine, (July-Aug., 1997 (1998)) Vol. 70, No. 4, pp. 403-408. print.
CODEN: YJBMAU. ISSN: 0044-0086. Language: English.

AB Previous studies suggested endotoxin, derived from the intestine through the portal blood to the liver, was predominantly metabolized by Kupffer cells. In the present study, fluorescent-labeled endotoxin injected into the rat portal vein was demonstrated not only in Kupffer cells but also in hepatocytes. Furthermore a great amount of labeled endotoxin was recovered in bile. In the livers of patients with primary biliary cirrhosis (PBC), immunohistochemistry demonstrated significant retention of endotoxin in the biliary epithelial cells, and treatment with ursodeoxycholic acid significantly reduced the retention in those cells. The study for detection of apoptosis demonstrated increased rates of apoptosis in hepatocytes and biliary epithelial cells in PBC liver, and the rate of apoptosis in biliary epithelial cells was significantly reduced after treatment with ursodeoxycholic acid.
Immunohistochemistry in PBC liver demonstrated significant reduction of fluorescence intensity for a 7H6 antigen in biliary epithelial cells, indicating the increased paracellular permeability of bile ducts, because cellular immunolocalization of that antigen has been shown to be inversely correlated with the paracellular permeability of the tight junction. These results suggest that, in biliary epithelial cells, retention of endotoxin, increased apoptosis, and increased permeability of tight junctions may be involved in the pathogenesis of PBC.

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=> s ursodeoxycholic acid and diuretics
L6          23 URSODEOXYCHOLIC ACID AND DIURETICS

=> dup remove l6
PROCESSING COMPLETED FOR L6
L7          16 DUP REMOVE L6 (7 DUPLICATES REMOVED)

=> d l7 1-16 cbib abs

L7   ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2006 ACS on STN
2005:14190   Document No. 142:100401  Composite product obtainable by
     co-grinding of an active principle with a N-vinyl-2-pyrrolidone/vinyl
     acetate copolymer.  Olivieri, Aldo; Bonanomi, Michele; Pazzi, Piergiorgio
     (Bioprogress S.p.A., Italy).  PCT Int. Appl. WO 2005000273 A1 20050106, 27
     pp.  DESIGNATED STATES: W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR,
     BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB,
     GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
     LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG,
     PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ,
     UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH,
     CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE,
     NL, PT, SE, SN, TD, TG, TR.  (English).  CODEN: PIXXD2.  APPLICATION: WO
     2003-IT401 20030627.
AB   The present invention describes a method for obtaining composite products
     comprising an active substance supported by a carrier, in which the
     carrier is the linear copolymer of N-vinyl-2-pyrrolidone (NVP) with vinyl
     acetate (VA).  The composite products are obtained by co-grinding of the
     dry mixture of the active substance and of the aforesaid carrier.  The
     composite products thus obtained have better physicochem. properties
     (lower melting enthalpy and/or lower melting temperature of the active
     substance) and a higher dissoln. speed with respect to composite products
     obtained with the same-co-grinding time with other carriers used in prior
     techniques.  Furthermore, the composite products obtained with the
     technique according to the present invention have the appearance of
     powders that are easier to work from a pharmaceutical point of view (flow,
     compression) with respect to composite products previously obtained with
     other carriers.  For example, 16.6 g of nimesulide were mixed with 49.8 g
     of NVP/VA for 15 min.  The powder was then poured into the grinding
     chamber of a low energy vibrational mill and the grinding was carried out
     for 2 h.

L7   ANSWER 2 OF 16  CAPLUS  COPYRIGHT 2006 ACS on STN
2005:36545   Document No. 142:107463  Treatment of liver disease with active
     vitamin D compounds.  Curd, John G. (Novacea, Inc., USA).  U.S. Pat. Appl.
     Publ. US 2005009793 A1 20050113, 14 pp., Cont.-in-part of Appl. No.
     PCT/US03/37291.  (English).  CODEN: USXXCO.  APPLICATION: US 2004-841606
     20040510.  PRIORITY: US 2002-427953P 20021121; WO 2003-US37291 20031121.
AB   The invention discloses a method for treating liver disease in an animal
     by administering an active vitamin D compound, preferably one that
     accumulates in the liver.

L7   ANSWER 3 OF 16  EMBASE  COPYRIGHT (c) 2006 Elsevier B.V. All rights
     reserved on STN
2005178483  EMBASE  Fatal course of parvovirus B19-associated myocarditis in a
     female liver transplant recipient. Jonetzko P.; Graziadei I.; Nachbaur K.;
     Vogel W.; Pankuweit S.; Zwick R.; Pachinger O.; Poelzl G.. Dr. P.
     Jonetzko, Clinical Division of Cardiology, Innsbruck Medical University,
     Anichstrasse 35, 6020 Innsbruck, Austria. patrycja.jonetzko@uklibk.ac.at.
     Liver Transplantation  Vol. 11, No. 4, pp. 463-466  2005.
     Refs: 17.
     ISSN: 1527-6465. CODEN: LITRFO
     Pub. Country: United Kingdom. Language: English. Summary Language:
     English.
     Entered STN: 20050505. Last Updated on STN: 20050505
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AB Acute myocarditis may result in severe hemodynamic compromise with fatal outcome. Furthermore, recent studies suggest myocarditis as a major cause of sudden unexpected death. A variety of cardiotropic viral, rickettsial, and bacterial infectious agents have been identified to date. Parvovirus B19 (PVB19) is usually benign in childhood, but it may also cause death due to myocarditis. We present here the case of an adult female who presented with fatigue, dyspnea on exertion, and orthostatic dizziness 8 months after successful liver transplantation. Cardiologic work-up, including left ventricular endomyocardial biopsy, revealed acute myocarditis secondary to PVB19. Since no specific therapy for this virus is available, the patient was treated symptomatically with an angiotensin-converting enzyme inhibitor plus beta-blocker and diuretics. After a period of stabilization, new-onset rapid atrial fibrillation caused acute low-output syndrome within 14 days after hospital admission. The patient eventually died because of refractory cardiogenic shock. In conclusion, to our knowledge this is the first report of PVB19-induced myocarditis confirmed by detection of viral genome in myocardium in a liver transplant recipient. Copyright .COPYRGT. 2005 by the American Association for the Study of Liver Diseases.

L7 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
2003:319266 Document No. 138:343857 Pharmaceutical formulations and systems for improved absorption and multistage release of active agents. Chen, Feng-Jing; Venkateshwaran, Srinivasan; Krill, Steven L.; Patel, Mahesh V. (USA). U.S. Pat. Appl. Publ. US 2003077297 A1 20030424, 55 pp., Cont.-in-part of U.S. Ser. No. 898,553. (English). CODEN: USXXCO. APPLICATION: US 2002-74687 20020211. PRIORITY: US 1999-258654 19990226; US 1999-345615 19990630; US 1999-447690 19991123; US 2001-800593 20010306; US 2001-877541 20010608; US 2001-898553 20010702.

AB The present invention pertains to pharmaceutical formulations and systems for delivery of active agents, wherein a first fraction of an active agent is suspended in a vehicle and a second fraction of active agent is solubilized in the vehicle, with the suspended fraction representing about 5 weight % to about 80 weight % of the active agent and the second fraction representing about 20 weight % to about 95 weight % of the active agent. One or more addnl. active agents, which may be fully solubilized, partially solubilized, or suspended, may also be present. The first and second fractions of the active agent may or may not have different release profiles. Generally, a significant fraction of the solubilized drug will release rapidly, providing for rapid onset, while the suspended drug may be formulated for delayed and/or sustained release. A pharmaceutical suspension contained isotretinoin 40, soybean oil 200, Maisine 35-1 100, and Lutrol F68 100 mg.

L7 ANSWER 5 OF 16 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
2003:577941 The Genuine Article (R) Number: 697XZ. Rational pharmacologic therapy of hepatobiliary disease in dogs and cats. Sartor L L (Reprint); Trepanier L A. Univ Wisconsin, Madison, WI 53706 USA (Reprint). COMPENDIUM ON CONTINUING EDUCATION FOR THE PRACTICING VETERINARIAN (JUN 2003) Vol. 25, No. 6, pp. 432-+. ISSN: 0193-1903. Publisher: VETERINARY LEARNING SYSTEMS, 425 PHILLIPS BLVD #100, TRENTON, NJ 08618 USA. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Treatment of hepatobiliary disease in dogs and cats,often involves the use of multiple drugs for their inflammatory, antifibrotic, cupruretic, hepatoprotectant, antimicrobial, diuretic, procoagulant, or antacid actions. This article reviews the indications for and optimal use of the following agents in the setting of hepatobiliary disorders of dogs and cats: glucocorticoids, azathioprine, colchicine, zinc, D-penicillamine, ursodiol, vitamin E, S-adenosyl-L-methionine, milk thistle (silymarin), carnitine and taurine, antimicrobials, lactulose, spironolactone and other diuretics, vitamin K-1, and gastrointestinal protectants.

L7 ANSWER 6 OF 16 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2003:582123 Document No.: PREV200300571970. DOES URSODEOXYCHOLIC ACID THERAPY ALTER THE PROFILE OF THE LIVER TRANSPLANT RECIPIENT WITH PRIMARY BILIARY CIRRHOSIS?. Gordon, Fiona [Reprint Author]; Muiesan, Paolo [Reprint Author]; Portmann, Bernard C. [Reprint Author]; Knisely, Alex S. [Reprint Author]; O'Donoghue, John [Reprint Author]; Rela, Mohammed [Reprint Author]; Heaton, Nigel D. [Reprint Author]; O'Grady, John G. [Reprint Author]. London, UK. Digestive Disease Week Abstracts and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. T1607. e-file. Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
Language: English.

AB Background Ursodeoxycholic acid (UDCA) therapy in primary biliary cirrhosis (PBC) improves the biochemical profile but may not slow histological progression or influence time to liver transplantation (LT). We aimed to determine whether UDCA therapy modified the clinical profile and/or pathway to liver transplantation. Methods PBC patients' clinical data were obtained from King's College Hospital Liver Transplant Database, comprising of prospectively collected records of all LTs performed between 1st February 1988 to 31st July 2001. UDCA therapy and pathology data were retrieved from case-notes. Patients who received UDCA for >2y pre-LT were used as a subgroup for comparison with those untreated. Wilcoxon signed rank and chi-squared tests were used to compare continuous and discrete variables, respectively. Results Data were available for 168 of 197 patients. Most were female (156; 93%) and the median age of all patients at LT was 54y (range 30-73y). 105 patients received no UDCA, but 63 (38%) received UDCA pre-LT for a mean of 2.3y (range 0.02-7.2y), at a mean dose of 10.2mg/kg/day (range 4.2-15), with 34 patients for >2y. The mean time from diagnosis to LT was 5.8y +/-4.4(SD) in UDCA-untreated patients, compared to 8.9y +/-5.2 in those on UDCA >2y (p=0.002), although the age at LT did not differ between groups. Significantly more UDCA >2y patients received diuretics pre-LT (53%; p=0.01) than those untreated (28%), but numbers with variceal bleeds, maximum encephalopathy scores, Child-Pugh scores and BMI-adjusted explant weights did not differ between groups. Mean serum bilirubin and alkaline phosphatase values at LT of patients on UDCA >2y were significantly lower than of those untreated (p=0.0001, p=0.004, respectively). Mean pre-LT international normalised ratio (INR) was lower in the >2y UDCA group (1.09 +/-0.15) than in untreated patients (1.3 +/-0.5; p=0.003). Platelet count, serum albumin and creatinine did not differ between groups. Differences in bilirubin, INR and use of diuretics remained significant (p<0.02) when all patients who received UDCA (n=63) were compared with those untreated. Conclusions The results suggest that there may be a shift from the characteristic cholestatic profile of PBC to one more typical of cirrhosis with UDCA therapy. Time from diagnosis to LT appears to have been delayed by UDCA therapy for >2y..

L7 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
2001:136991 Document No. 134:198075 Triglyceride-free compositions and methods for enhanced absorption of hydrophilic therapeutic agents. Patel, Mahesh V.; Chen, Feng-Jing (Lipocine, Inc., USA). PCT Int. Appl. WO 2001012155 A1 20010222, 113 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2.
APPLICATION: WO 2000-US18807 20000710. PRIORITY: US 1999-375636 19990817.

AB The present invention relates to triglyceride-free pharmaceutical compns., pharmaceutical systems, and methods for enhanced absorption of hydrophilic therapeutic agents. The compns. and systems include an absorption enhancing carrier, where the carrier is formed from a combination of at least two surfactants, at least one of which is hydrophilic. A hydrophilic therapeutic agent can be incorporated into the composition, or can be co-administered with the composition as part of a pharmaceutical system. The invention also provides methods of treatment with hydrophilic therapeutic agents using these compns. and systems. For example, when a composition containing Cremophor RH40 0.30, Arlacel 186 0.20, Na taurocholate 0.18, and propylene glycol 0.32 g, resp., was used, the relative absorption of PEG 4000 as a model macromol. drug was enhanced by 991%.

L7 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
2001:101167 Document No. 134:168315 Enhancement of bioavailability of peptides with bile salts. Morrison, James Duncan; Lucas, Michael Leslie; Wheeler, Sarah (The University Court of the University of Glasgow, UK). PCT Int. Appl. WO 2001009163 A2 20010208, 28 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-GB2903 20000728. PRIORITY: GB 1999-17793 19990730.

AB The present invention relates to improving and/or increasing the bioavailability of a biol. active substance, such as a peptide. In particular the present invention relates to the conjugation of the biol. active substance to a bile acid. The conjugated biol. active substance is suitable particularly for oral or parental administration. Illeal administration of 600μg/kg gastrin tetrapeptide conjugated to cholate resulted in a significant mean increase in gastric acid secretion of 1.84 μmol over a 3 h collection period, while no increase in acid secretion was noticed by administration of tetragastrin alone or with sep. cholate.

L7 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
2000:645885 Document No. 133:217694 Endotoxin-modulating compounds for therapy of heart failure and cachexia. Anker, Stefan; Coats, Andrew; Volk, Hans-Dieter; Rauchhaus, Mathias; Schumann, Ralf Reiner (Max-Delbruck-Centrum fur Molekulare Medizin, Germany). PCT Int. Appl. WO 2000053224 A2 20000914, 74 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP2299 20000309. PRIORITY: GB 1999-5300 19990309; GB 1999-5307 19990309; GB 1999-5310 19990309; GB 1999-5314 19990309; GB 1999-5315 19990309.

AB A method of treating, preventing or ameliorating chronic or acute heart failure in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, bile acids, or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or

endotoxin (LPS) from the gut into the patient's circulation. A method of treating, preventing or ameliorating endotoxin-mediated immune activation in acute or chronic heart failure in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, bile acids or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. Also disclosed is a method for treating cachexia and wasting syndromes due to diseases other than congestive heart failure.

L7 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
2000:277810 Document No. 132:326056 Systems for oral delivery. Russell-Jones, Gregory John (Biotech Australia Pty. Ltd., Australia). PCT Int. Appl. WO 2000022909 A2 20000427, 32 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-IB1872 19991018. PRIORITY: US 1998-PV104827 19981019.

AB A pharmaceutical and a biol. active substance, for oral administration, can be "coated" or "encapsulated" with a carboxylic acid, such that the substance is protected from proteolysis in the stomach and is taken up from the intestine. It is thought that the carboxylic acids coat and protect the active agent from the proteolytic environment of the stomach, allowing the agent to pass safely through the stomach and to be absorbed in the small intestines. The carboxylic acid agent complex can be adopted for oral, nasal, buccal, and transdermal delivery of moderately soluble and even insol. bioactive agents.

L7 ANSWER 11 OF 16 MEDLINE on STN DUPLICATE 1
1999449169. PubMed ID: 10520859. A pilot study on the hemodynamic effect of short-term ursodeoxycholic acid therapy in patients with stable liver cirrhosis. Baruch Y; Assy N; Weisbruch F; Reisner S A; Rinkevich D; Enat R; Blendis L M; Bomzon A. (Department of Medicine Band Cardiology, Rambam Medical Center, Haifa, Israel.) The American journal of gastroenterology, (1999 Oct) Vol. 94, No. 10, pp. 3000-4. Journal code: 0421030. ISSN: 0002-9270. Pub. country: United States. Language: English.

AB OBJECTIVE: Total serum bile acid concentrations are elevated in individuals with liver disease. Ursodeoxycholic acid (UDCA) therapy in such patients results in a further significant rise in plasma levels to the extent that it becomes the major circulating bile acid. In laboratory animals, bile acids, such as taurocholic acid, have also been shown to possess a diuretic-like action, as they can promote diuresis, natriuresis, and kaliuresis by inhibiting tubular sodium reabsorption. The aim of the present study was to assess the effect of 1 month's UDCA therapy on cardiovascular function in cirrhotic patients. METHODS: Two groups of patients with cirrhosis were studied, six with primary biliary cirrhosis (PBC) and six with postnecrotic liver cirrhosis (PNC). Cardiovascular function was assessed by determination of blood pressure, heart rate, and by two-dimensional and pulsed Doppler echocardiography. RESULTS: In PBC patients, 1 month's treatment with UDCA significantly reduced diastolic volume without changing systolic, diastolic, and mean blood pressures, heart rate, systolic and stroke

volumes, ejection fraction, cardiac output, and systemic vascular resistance. In PNC patients, UDCA significantly reduced cardiac output, with a tendency to reduce left ventricular volumes, without any changes in systolic, diastolic, and mean blood pressures. CONCLUSIONS: UDCA caused reductions in diastolic volume in the PBC patients and cardiac output in the PNC patients. Such reductions are not unlike that seen in individuals treated with diuretics. This diuretic-like action deserves further study, particularly in cirrhotic patients who are also being treated with diuretics or show evidence of cardiac myopathy.

L7 ANSWER 12 OF 16 MEDLINE on STN
97309587. PubMed ID: 9167002. Effect of niuche-shen-qi-wan on painful muscle cramps in patients with liver cirrhosis: a preliminary report. Motoo Y; Taga H; Yamaguchi Y; Watanabe H; Okai T; Sawabu N. (Department of Internal Medicine, Kanazawa University, Japan.) The American journal of Chinese medicine, (1997) Vol. 25, No. 1, pp. 97-102. Journal code: 7901431. ISSN: 0192-415X. Pub. country: United States. Language: English.
AB Twelve patients with liver cirrhosis complaining of painful muscle cramps were treated with Niuche-Shen-Qi-Wan (TJ-107). Three patients were at the decompensated state. Muscle cramps disappeared in 4 weeks on the average after oral administration of TJ-107 in all 12 patients. During the period of TJ-107 administration, there was no significant improvement of hepatic function. One patient complained of mild epigastric discomfort after taking TJ-107, but there were no other adverse effects. Our results indicate that TJ-107 is useful for treatment of painful muscle cramps in cirrhotic patients.

L7 ANSWER 13 OF 16 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 2
91074895 EMBASE Document No.: 1991074895. Pathophysiology and clinical basis of prevention and treatment of complications of chronic liver disease. Wagner S.; Lautz H.-U.; Muller M.J.; Schmidt F.W.. Gastroenterologie/Hepatologie, Medizinische Hochschule, Konstanty-Gutschow-Str. 8,3000 Hannover 61, Germany. Klinische Wochenschrift Vol. 69, No. 3, pp. 112-120 1991.
ISSN: 0023-2173. CODEN: KLWOAZ
Pub. Country: Germany. Language: English. Summary Language: English.
Entered STN: 911216. Last Updated on STN: 911216
AB Chronic liver failure is characterized by the appearance of jaundice, ascites, encephalopthy and/or gasrointestinal bleeding. Acute episodes of hepatic decompensation are fequently precipitated by additional events, e.g. septicaemia, diuretic therapy or excessive protein intake. Identification, correction and treatment of these precipitating factors are first steps in the management of chronic liver failure. Nutritional support is important in the treatment of cirrhotic patients, because malnutrition is one of the major determinants of patient outcome. Management of encephalopathy reduces the appearance of gut-derived nitrogenous toxins and corrects imbalances in amino acid metabolism. Treatment of ascites is salt restriction supported by gentle and incremental administration of diuretics. Ursodesoxycholic acid has become a new and promising modality in the management of cholestatic liver diseases. If conservative therapy fails to recompensate liver function, liver transplantation may be indicated.

L7 ANSWER 14 OF 16 MEDLINE on STN DUPLICATE 3
91184032. PubMed ID: 2081480. Traditional management of liver disorders. Messner M; Brissot P. (Liver Unit, Pontchaillou Hospital, Rennes, France.) Drugs, (1990) Vol. 40 Suppl 3, pp. 45-57. Ref: 148. Journal code: 7600076. ISSN: 0012-6667. Pub. country: United States. Language: English.
AB Dietary measures have achieved mixed results in the management of liver disorders. Although a high energy diet may shorten the course of viral hepatitis by a relatively small amount, dietary restriction is usually of no benefit in compensated cirrhosis. Restriction of sodium intake to 22 to 60 mol/day leads to resolution of cirrhotic ascites in approximately

20% of patients, and reduces the requirement for diuretics in the remainder. In advanced liver disease, diet plays an important role in the avoidance of portal-systemic encephalopathy (PSE), with the tolerance of most nutrients, most importantly protein, being sharply reduced. Despite the frequent presence of carbohydrate intolerance in liver disease, carbohydrate supplementation may be required to ensure adequate utilisation of the reduced dietary protein intake. Zinc supplementation may also be required in liver cirrhosis to compensate for a deficiency. Bed rest is an important component of the management of acute and chronic liver disorders, together with the avoidance of fatigue. Abstinence from alcohol is required in alcoholic liver disease patients, who should receive parenteral thiamine 100 mg and other vitamin and mineral supplementation as required. Agents acting on the ascending loop of Henle [such as furosemide (frusemide)] or the distal tubule (such as spironolactone) are the diuretics most frequently employed to mobilise ascites in cirrhosis, the latter drug being the more effective in nonazotaemic patients. In the absence of oedema, the diuresis should be restricted to a maximum of 750 ml/day; however, patients with oedema may safely undergo a diuresis of less than or equal to 1.5 L/day. Diuretic therapy is often associated with renal complications, such as azotaemia (usually reversible) and severe hyponatraemia in cirrhotic patients with ascites; spironolactone may produce antiandrogenic adverse effects. Lactulose, used in the treatment of acute and chronic PSE, acts by inhibiting gastrointestinal absorption of ammonia and other toxic nitrogenous substances, and by reducing urea degradation. Other pharmacological treatments, such as branched-chain amino acids and benzodiazepine antagonists have a limited role in the management of PSE. Chronic cholestasis has been treated with cholestyramine and fat-soluble vitamins, whereas ursodeoxycholic acid appears to be a promising agent in the treatment of primary biliary cirrhosis. In chronic hepatitis, the prevention of development of cirrhosis is a primary treatment goal which has been attempted with variable success using antifibrotic drugs such as penicillamine and colchicine.(ABSTRACT TRUNCATED AT 400 WORDS)

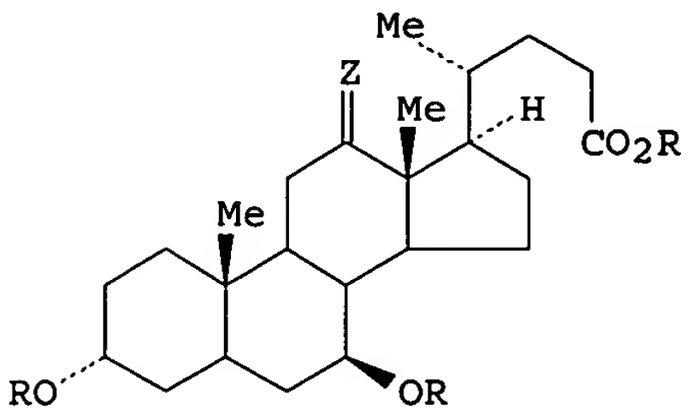
L7 ANSWER 15 OF 16 MEDLINE on STN

86219857. PubMed ID: 2872047. The effect of drugs on bile flow and composition. An overview. Okolicsanyi L; Lirussi F; Strazzabosco M; Jemmolo R M; Orlando R; Nassuato G; Muraca M; Crepaldi G. Drugs, (1986 May) Vol. 31, No. 5, pp. 430-48. Ref: 165. Journal code: 7600076. ISSN: 0012-6667. Pub. country: Australia. Language: English.

AB Many drugs are eliminated via the hepatobiliary route, after biotransformation in the liver. Some of them may affect bile flow and/or the hepatic secretion of biliary lipids such as bile acids, cholesterol and phospholipids. Bile acids are the most potent agents which increase bile flow, especially unconjugated bile acids. Other drugs which increase bile flow include phenobarbitone (phenobarbital), theophylline, glucagon and insulin. In contrast, ethacrynic acid, amiloride, ouabain, oestrogens and chlorpromazine are among those agents which decrease bile flow. Biliary bile acid secretion is altered by a variety of drugs, including cheno- and ursodeoxycholic acids (CDCA and UCDA), the bile acid sequestrants cholestyramine and colestipol, and ethinyloestradiol. The composition of bile can also be altered by drug therapy. Thus, clofibrate increases biliary cholesterol secretion, and reduces bile acid concentrations, without altering biliary phospholipid concentrations. However, other clofibrate derivatives may produce changes of a different pattern, suggesting that the risk of developing gallstones may differ for each derivative. Nicotinic acid and d-thyroxine also increase biliary cholesterol saturation, while CDCA and UDCA reduce biliary cholesterol concentration. The potential consequences of drug-induced changes in bile flow and composition extend to the liver, the gallbladder and the intestine. If adverse effects are to be avoided, further study in this often overlooked area is required.

L7 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
1983:126470 Document No. 98:126470 High purity ursodeoxycholic acid. Bonaldi, Antonio; Molinari, Egidio (Erregierre S.p.A., Italy). Eur. Pat. Appl. EP 63106 A1 19821020, 20 pp. DESIGNATED STATES: R: AT, BE, CH, DE, FR, GB, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1982-830083 19820405. PRIORITY: IT 1981-21137 19810414.

GI



I

AB Ursodeoxycholic acid (I; R = H; Z = H2) (II) was prepared from I (R = H, Me3Si; Z = O) by reduction with N2H4 in the presence of an alkaline base and triethylene glycol and subsequent desilylation. II is useful in the treatment of biliary calculi and as an anticholesteremic and diuretic agent (no data).

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=> s composition
L8     3239616 COMPOSITION

=> s l8 and ursodeoxycholic acid
L9        1310 L8 AND URSODEOXYCHOLIC ACID

=> s l9 and diuretics
L10          2 L9 AND DIURETICS

=> dup remove l10
PROCESSING COMPLETED FOR L10
L11          2 DUP REMOVE L10 (0 DUPLICATES REMOVED)

=> d l11 1-2 cbib abs

L11 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN
2001:136991 Document No. 134:198075 Triglyceride-free compositions
and methods for enhanced absorption of hydrophilic therapeutic agents.
Patel, Mahesh V.; Chen, Feng-Jing (Lipocine, Inc., USA). PCT Int. Appl.
WO 2001012155 A1 20010222, 113 pp. DESIGNATED STATES: W: AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM,
DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,
KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE,
BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT,
LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2.
APPLICATION: WO 2000-US18807 20000710. PRIORITY: US 1999-375636 19990817.
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AB The present invention relates to triglyceride-free pharmaceutical compns., pharmaceutical systems, and methods for enhanced absorption of hydrophilic therapeutic agents. The compns. and systems include an absorption enhancing carrier, where the carrier is formed from a combination of at least two surfactants, at least one of which is hydrophilic. A hydrophilic therapeutic agent can be incorporated into the compn., or can be co-administered with the compn. as part of a pharmaceutical system. The invention also

provides methods of treatment with hydrophilic therapeutic agents using these compns. and systems. For example, when a compn. containing Cremophor RH40 0.30, Arlacel 186 0.20, Na taurocholate 0.18, and propylene glycol 0.32 g, resp., was used, the relative absorption of PEG 4000 as a model macromol. drug was enhanced by 991%.

L11 ANSWER 2 OF 2 MEDLINE on STN

86219857. PubMed ID: 2872047. The effect of drugs on bile flow and composition. An overview. Okolicsanyi L; Lirussi F; Strazzabosco M; Jemmolo R M; Orlando R; Nassuato G; Muraca M; Crepaldi G. Drugs, (1986 May) Vol. 31, No. 5, pp. 430-48. Ref: 165. Journal code: 7600076. ISSN: 0012-6667. Pub. country: Australia. Language: English.

AB Many drugs are eliminated via the hepatobiliary route, after biotransformation in the liver. Some of them may affect bile flow and/or the hepatic secretion of biliary lipids such as bile acids, cholesterol and phospholipids. Bile acids are the most potent agents which increase bile flow, especially unconjugated bile acids. Other drugs which increase bile flow include phenobarbitone (phenobarbital), theophylline, glucagon and insulin. In contrast, ethacrynic acid, amiloride, ouabain, oestrogens and chlorpromazine are among those agents which decrease bile flow. Biliary bile acid secretion is altered by a variety of drugs, including cheno- and ursodeoxycholic acids (CDCA and UCDA), the bile acid sequestrants cholestyramine and colestipol, and ethinyloestradiol. The composition of bile can also be altered by drug therapy. Thus, clofibrate increases biliary cholesterol secretion, and reduces bile acid concentrations, without altering biliary phospholipid concentrations. However, other clofibrate derivatives may produce changes of a different pattern, suggesting that the risk of developing gallstones may differ for each derivative. Nicotinic acid and d-thyroxine also increase biliary cholesterol saturation, while CDCA and UDCA reduce biliary cholesterol concentration. The potential consequences of drug-induced changes in bile flow and composition extend to the liver, the gallbladder and the intestine. If adverse effects are to be avoided, further study in this often overlooked area is required.

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=> s l9 and UCDA
L12           8 L9 AND UCDA

=> dup remove l12
PROCESSING COMPLETED FOR L12
L13           4 DUP REMOVE L12 (4 DUPLICATES REMOVED)

=> d l13 1-4 cbib abs
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L13 ANSWER 1 OF 4 MEDLINE on STN DUPLICATE 1

2002440604. PubMed ID: 12198643. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. Paumgartner Gustav; Beuers Ulrich. (Department of Medicine II, Klinikum Grosshadern, University of Munich, Munich, Germany.. Gustav.Paumgartner@med2.med.uni-muenchen.de) . Hepatology (Baltimore, Md.), (2002 Sep) Vol. 36, No. 3, pp. 525-31. Ref: 55. Journal code: 8302946. ISSN: 0270-9139. Pub. country: United States. Language: English.

AB Ursodeoxycholic acid (UCDA) is increasingly used for the treatment of cholestatic liver diseases. Experimental evidence suggests three major mechanisms of action: (1) protection of cholangiocytes against cytotoxicity of hydrophobic bile acids, resulting from modulation of the composition of mixed phospholipid-rich micelles, reduction of bile acid cytotoxicity of bile and, possibly, decrease of the concentration of hydrophobic bile acids in the cholangiocytes; (2) stimulation of hepatobiliary secretion, putatively via Ca(2+)- and protein kinase C-alpha-dependent mechanisms and/or activation of p38(MAPK) and extracellular signal-regulated kinases (Erk) resulting in insertion of transporter molecules (e.g., bile salt export pump, BSEP, and

conjugate export pump, MRP2) into the canalicular membrane of the hepatocyte and, possibly, activation of inserted carriers; (3) protection of hepatocytes against bile acid-induced apoptosis, involving inhibition of mitochondrial membrane permeability transition (MMPT), and possibly, stimulation of a survival pathway. In primary biliary cirrhosis, UDCA (13-15 mg/kg/d) improves serum liver chemistries, may delay disease progression to severe fibrosis or cirrhosis, and may prolong transplant-free survival. In primary sclerosing cholangitis, UDCA (13-20 mg/kg/d) improves serum liver chemistries and surrogate markers of prognosis, but effects on disease progression must be further evaluated. Anticholestatic effects of UDCA have also been reported in intrahepatic cholestasis of pregnancy, liver disease of cystic fibrosis, progressive familial intrahepatic cholestasis, and chronic graft-versus-host disease. Future efforts will focus on definition of additional clinical uses of UDCA, on optimized dosage regimens, as well as on further elucidation of mechanisms of action of UDCA at the molecular level.

L13 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
1993:99482 Document No. 118:99482 Diurnal variation in cholesterol metastability of hepatic bile and its acute modulation with ursodeoxycholic acid in humans. Noshiro, Hirokazu; Chijiiwa, Kazuo; Hirota, Ichio (Fac. Med., Kyushu Univ., Fukuoka, 812, Japan). Journal of Hepatology, 16(1-2), 23-30 (English) 1992. CODEN: JOHEEC. ISSN: 0168-8278.

AB The authors studied the alteration of cholesterol metastability of hepatic bile caused by diurnal variations in hepatic biliary lipid excretions and acutely induced changes following ursodeoxycholic acid (UCDA) administration. Hepatic bile was collected at 6-h intervals for 24 h from 6 patients with an indwelling choledochal drainage before and after UDCA administration. A basal diurnal variation showed the highest cholesterol saturation index and cholesterol distribution in vesicles and the shortest nucleation time in the early morning. After the ingestion of ursodeoxycholic acid for 1 day, early morning biliary cholesterol concns. were reduced. Interestingly, decreases in vesicular cholesterol concns. (1.0 to 0.1 mM) and in the vesicular cholesterol/phospholipid ratio (1.6 to 0.7) were associated with prolongation of the nucleation time (11.5 to 18.7 days. Biliary protein had no diurnal variations and did not decrease with UCDA. These results indicate that during a day the early morning hepatic bile is the most unstable and that UCDA acutely enhances hepatic biliary metastability mainly by decreasing the rate of vesicular cholesterol saturation

L13 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 2
86219857. PubMed ID: 2872047. The effect of drugs on bile flow and composition. An overview. Okolicsanyi L; Lirussi F; Strazzabosco M; Jemmolo R M; Orlando R; Nassuato G; Muraca M; Crepaldi G. Drugs, (1986 May) Vol. 31, No. 5, pp. 430-48. Ref: 165. Journal code: 7600076. ISSN: 0012-6667. Pub. country: Australia. Language: English.

AB Many drugs are eliminated via the hepatobiliary route, after biotransformation in the liver. Some of them may affect bile flow and/or the hepatic secretion of biliary lipids such as bile acids, cholesterol and phospholipids. Bile acids are the most potent agents which increase bile flow, especially unconjugated bile acids. Other drugs which increase bile flow include phenobarbitone (phenobarbital), theophylline, glucagon and insulin. In contrast, ethacrynic acid, amiloride, ouabain, oestrogens and chlorpromazine are among those agents which decrease bile flow. Biliary bile acid secretion is altered by a variety of drugs, including cheno- and ursodeoxycholic acids (CDCA and UCDA), the bile acid sequestrants cholestyramine and colestipol, and ethinyloestradiol. The composition of bile can also be altered by drug therapy. Thus, clofibrate increases biliary cholesterol secretion, and reduces bile acid concentrations, without altering biliary phospholipid concentrations. However, other clofibrate derivatives may produce changes of a different pattern, suggesting that the risk of

developing gallstones may differ for each derivative. Nicotinic acid and d-thyroxine also increase biliary cholesterol saturation, while CDCA and UDCA reduce biliary cholesterol concentration. The potential consequences of drug-induced changes in bile flow and composition extend to the liver, the gallbladder and the intestine. If adverse effects are to be avoided, further study in this often overlooked area is required.

L13 ANSWER 4 OF 4 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

78251160 EMBASE Document No.: 1978251160. Comparative effects of ursodeoxycholic acid and chenodeoxycholic acid in the rhesus monkey. Biochemical and ultrastructural studies. Fedorowski T.; Salen G.; Zaki F.G.; et al.. Gastroenterol. Sect., VA Hosp., East Orange, N.J. 07019, United States. Gastroenterology Vol. 74, No. 1, pp. 75-81 1978.

CODEN: GASTAB

Pub. Country: United States. Language: English.

AB To investigate the effects of bile acid feeding on hepatic function, rhesus monkeys were treated with 40 and 100 mg per kg day of ursodeoxycholic acid (UCDA) (3α,7β-dihydroxycholanoic acid) and chenodeoxycholic acid (CDCA) (3α,7α-dihydroxycholanoic acid), respectively. Serum transaminases (SGOT, SGPT) and leucine aminopeptidase levels were measured at the start of the studies, at monthly intervals thereafter, and terminally. After 6 months, all animals were killed and hepatic morphology was examined by light and electron microscopy; biliary bile acid composition and fecal bile composition were determined by gas-liquid chromatography. Liver damage developed in the CDCA-treated animals and consisted of bile duct proliferation, periportal inflammation, fibrosis and disruption of bile canaliculi, and was associated with a 4- to 10-fold rise in serum transaminase and leucine aminopeptidase levels. Biliary lithocholic acid rose to 10% of the total biliary bile acids in the CDCA-treated animals. In contrast, liver morphology aand function tests were not affected by either 40 or 100 mg per kg per day of UDCA; biliary lithocholic acid concentrations did not change appreciably. Hepatic β-hydroxy-β-methylglutaryl coenzyme A reductase activity reflecting cholesterogenesis was suppressed equally (30%) by UDCA and CDCA, but serum cholesterol levels did not change. These findings confirm that CDCA is associaed with serious liver damage that probably results from increased formation of lithocholic acid. In contrast, UDCA caused no liver toxicity and no rise in lithocholic acid. Thus, the 7β-hydroxy group of UDCA was apparently degraded differently than the 7α-hydroxy group of CDCA, suggesting that intestinal bacterial dehydroxylases are stereospecific. Because of different bacterial degradation, gallstone treatment with UDCA may be safer and more economical.

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=> s heart failure
L14     312219 HEART FAILURE

=> s l14 and LPS
L15        341 L14 AND LPS

=> s l15 and treatment
L16        111 L15 AND TREATMENT

=> s l6 and UCDA
L17          1 L6 AND UCDA

=> d l17 cbib abs

L17  ANSWER 1 OF 1     MEDLINE on STN
86219857.    PubMed ID: 2872047.   The effect of drugs on bile flow and
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composition. An overview. Okolicsanyi L; Lirussi F; Strazzabosco M; Jemmolo R M; Orlando R; Nassuato G; Muraca M; Crepaldi G. Drugs, (1986 May) Vol. 31, No. 5, pp. 430-48. Ref: 165. Journal code: 7600076. ISSN: 0012-6667. Pub. country: Australia. Language: English.

AB Many drugs are eliminated via the hepatobiliary route, after biotransformation in the liver. Some of them may affect bile flow and/or the hepatic secretion of biliary lipids such as bile acids, cholesterol and phospholipids. Bile acids are the most potent agents which increase bile flow, especially unconjugated bile acids. Other drugs which increase bile flow include phenobarbitone (phenobarbital), theophylline, glucagon and insulin. In contrast, ethacrynic acid, amiloride, ouabain, oestrogens and chlorpromazine are among those agents which decrease bile flow. Biliary bile acid secretion is altered by a variety of drugs, including cheno- and ursodeoxycholic acids (CDCA and UCDA), the bile acid sequestrants cholestyramine and colestipol, and ethinyloestradiol. The composition of bile can also be altered by drug therapy. Thus, clofibrate increases biliary cholesterol secretion, and reduces bile acid concentrations, without altering biliary phospholipid concentrations. However, other clofibrate derivatives may produce changes of a different pattern, suggesting that the risk of developing gallstones may differ for each derivative. Nicotinic acid and d-thyroxine also increase biliary cholesterol saturation, while CDCA and UDCA reduce biliary cholesterol concentration. The potential consequences of drug-induced changes in bile flow and composition extend to the liver, the gallbladder and the intestine. If adverse effects are to be avoided, further study in this often overlooked area is required.

```
=> s l16 and diuretic
L18           2 L16 AND DIURETIC

=> dup remove l18
PROCESSING COMPLETED FOR L18
L19           2 DUP REMOVE L18 (0 DUPLICATES REMOVED)

=> d l19 1-2 cbib abs

L19  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
2000:513526  Document No. 133:134187  Method of treating chronic cardiac
     disease.  Giroir, Brett P.; Scannon, Patrick J. (Xoma Technology Ltd.,
     USA; Board of Regents, the University of Texas System).  PCT Int. Appl. WO
     2000043028 A2 20000727, 36 pp.  DESIGNATED STATES: W:  AE, AL, AM, AT, AU,
     AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI,
     GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
     LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO,
     RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
     ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG,
     CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR,
     NE, NL, PT, SE, SN, TD, TG.  (English).  CODEN: PIXXD2.  APPLICATION: WO
     2000-US1515 20000121.  PRIORITY: US 1999-PV116736 19990122.
AB   New therapeutic uses for bactericidal/permeability-increasing (BPI)
     protein products that involve treatment of chronic cardiac
     disease.  The chronic cardiac diseases include chronic congestive
     heart failure, cardiomyopathy, and congenital heart
     defect.  The patients with chronic cardiac disease exhibit elevated level
     of circulating LPS and LBP.

L19  ANSWER 2 OF 2  SCISEARCH  COPYRIGHT (c) 2006 The Thomson Corporation  on
     STN
1999:428306  The Genuine Article (R) Number: 202TG. Endotoxin and immune
     activation in chronic heart failure: a prospective
     cohort study.  Niebauer J; Volk H D; Kemp M; Dominguez M; Schumann R R;
     Rauchhaus M; Poole-Wilson P A; Coats A J S; Anker S D (Reprint). Natl
     Heart & Lung Inst, Imperial Coll Sch Med, Dovehouse St, London SW3 6LY,
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England (Reprint); Natl Heart & Lung Inst, Imperial Coll Sch Med, London SW3 6LY, England; Univ Leipzig, Herzzentrum, Leipzig, Germany; Univ Klinikum Charite, Inst Med Immunol, Berlin, Germany; Harefield Hosp, Heart Sci Ctr, Harefield, Middx, England; Univ Klinikum Charite, Inst Mikrobiol & Hyg, Berlin, Germany; Max Delbruck Ctr Mol Med, Franz Volhard Klin, Berlin, Germany. LANCET (29 MAY 1999) Vol. 353, No. 9167, pp. 1838-1842. ISSN: 0140-6736. Publisher: LANCET LTD, 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background. Immune activation in patients with chronic heart failure may be secondary to endotoxin (lipopolysaccharide) action. We investigated the hypothesis that altered gut permeability with bacterial translocation and endotoxaemia would be increased in patients with oedema secondary to congestive heart failure.

Methods. We compared 20 patients who had chronic heart failure with recent-onset peripheral oedema (mean age 64 years [SD 10], New York Heart Association [NYHA] class 3.3 [0.7]), 20 stable non-oedematous patients with chronic heart failure (mean age 63 years [19], NYHA class 2.6 [0.7]), and 14 healthy volunteers (mean age 55 years [16]). Biochemical markers of endotoxaemia, inflammation, and immune activation were measured. Ten patients were studied within 1 week of complete resolution of oedema. Five patients survived longer than 6 months and were restudied again after remaining free of oedema for more than 3 months.

Findings. Mean endotoxin concentrations were higher in oedematous patients with chronic heart failure than in stable patients with chronic heart failure (0.74 [SD 0.45] vs 0.37 EU/mL [0.23], p = 0.0009) and controls (0.46 EU/mL [0.21], p = 0.02). Oedematous patients had the highest concentrations of several cytokines. After short-term diuretic treatment, endotoxin concentrations decreased from 0.84 EU/mL [0.49] to 0.45 EU/mL [0.21], p < 0.05) but cytokines remained raised. After freedom of oedema for more than 3 months after oedema resolved, endotoxin concentrations remained unchanged from the previous visit (0.49 EU/mL [0.06], p = 0.45).

Interpretation. Raised concentrations of endotoxin and cytokines are found in patients with chronic heart failure during acute oedematous exacerbation. Intensified diuretic treatment can normalise endotoxin concentrations. Our preliminary findings suggest that endotoxin may trigger immune activation in patients with chronic heart failure during oedematous episodes.

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=> s l16 and ursodeoxycholic acid
L20             0 L16 AND URSODEOXYCHOLIC ACID

=> s (anker s?/au or coats a?/au or volk h?/au or rauchhaus m?/au or schumann r?/au)
L21          7575 (ANKER S?/AU OR COATS A?/AU OR VOLK H?/AU OR RAUCHHAUS M?/AU OR
                  SCHUMANN R?/AU)

=> s l21 and ursodeoxycholic acid
L22             5 L21 AND URSODEOXYCHOLIC ACID

=> dup remove l22
PROCESSING COMPLETED FOR L22
L23             3 DUP REMOVE L22 (2 DUPLICATES REMOVED)

=> d l23 1-3 cbib abs

L23  ANSWER 1 OF 3     MEDLINE on STN                          DUPLICATE 1
2004410934.    PubMed ID: 15315599.   Cholestasis of pregnancy, pruritus and
     5-hydroxytryptamine 3 receptor antagonists. Schumann Roman;
     Hudcova Jana. (Department of Anesthesia, Tufts University School of
     Medicine, Tufts-New England Medical Center, Boston, MA 02111, USA..
     Rschumann@tufts-nemc.org) . Acta obstetricia et gynecologica Scandinavica,
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(2004 Sep) Vol. 83, No. 9, pp. 861-2. Journal code: 0370343. ISSN: 0001-6349. Pub. country: Denmark. Language: English.

AB Pruritus, an early symptom of intrahepatic cholestasis of pregnancy, may be severe. Conventional treatment includes ursodeoxycholic acid and cholestyramine. Ondansetron, a 5-hydroxytryptamine 3 receptor antagonist antiemetic, has been shown to reduce pruritus of different etiologies including cholestasis. We now report the successful preoperative use of ondansetron in a patient with pruritus from intrahepatic cholestasis of pregnancy. While the mechanism for our patient's response is poorly understood, 5-hydroxytryptamine 3 receptor antagonists should be further evaluated and possibly considered as a treatment option for intrahepatic cholestasis of pregnancy-related pruritus.

L23 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN

2000:645885 Document No. 133:217694 Endotoxin-modulating compounds for therapy of heart failure and cachexia. Anker, Stefan; Coats, Andrew; Volk, Hans-Dieter; Rauchhaus, Mathias; Schumann, Ralf Reiner (Max-Delbruck-Centrum fur Molekulare Medizin, Germany). PCT Int. Appl. WO 2000053224 A2 20000914, 74 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP2299 20000309. PRIORITY: GB 1999-5300 19990309; GB 1999-5307 19990309; GB 1999-5310 19990309; GB 1999-5314 19990309; GB 1999-5315 19990309.

AB A method of treating, preventing or ameliorating chronic or acute heart failure in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, bile acids, or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. A method of treating, preventing or ameliorating endotoxin-mediated immune activation in acute or chronic heart failure in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, bile acids or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. Also disclosed is a method for treating cachexia and wasting syndromes due to diseases other than congestive heart failure.

L23 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN

2000:645835 Document No. 133:217707 Therapy of cachexia and wasting syndromes with bile acids. Anker, Stefan; Coats, Andrew ; Volk, Hans-dieter; Schumann, Ralf Reiner; Plauth, Mathias; Lochs, Herbert (Max-Delbruck-Centrum fur Molekulare Medizin, Germany). PCT Int. Appl. WO 2000053165 A2 20000914, 26 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,

IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG.
(English). CODEN: PIXXD2. APPLICATION: WO 2000-EP2062 20000309.
PRIORITY: GB 1999-5315 19990309; GB 1999-5300 19990309; GB 1999-5310 19990309; GB 1999-5307 19990309; GB 1999-5314 19990309.

AB The present invention relates to therapy and the use of agents in the therapy of cachexia and wasting syndromes due to diseases other than congestive heart failure. Cachexia occurs in a number of other chronic diseases, like liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, and rheumatoid arthritis. Cachexia and weight loss are linked to inflammatory processes and they are linked to increased mortality and/or morbidity. Cytokine activation is a potential causal mechanism for the development of cachexia also in these other diseases. The invention describes a method of treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis in a patient. The method comprises administering to the patient an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; LPS). The invention describes also a method of treating, preventing or ameliorating endotoxin-mediated immune activation in body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis. The method comprises administering to the patient an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; LPS). The ability of ursodeoxycholic acid and BPI protein to inhibit LPD-mediated NFT production in the whole blood of patients with cachexia is shown.